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STRATEGY FOR THE SYNTHESIS OF THE C_{10}-C_{19} PORTION OF AMPHIDINOLIDE-A

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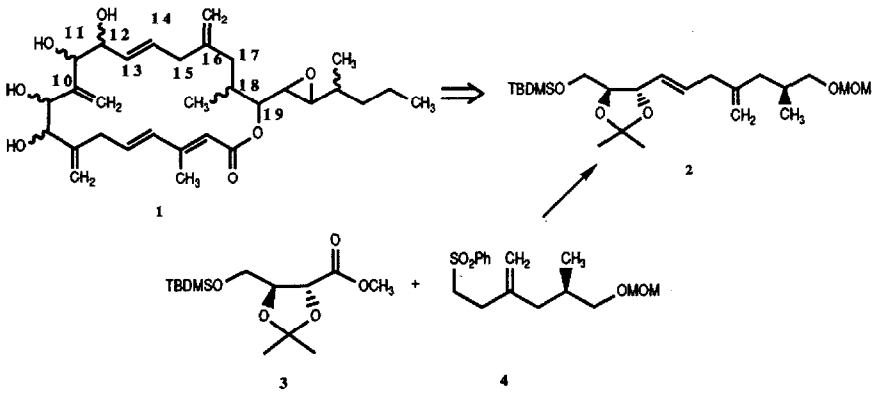
Abstract: A stereospecific synthesis of a potential C10-C19 fragment of the novel antineoplastic macrolide amphidinolide-A is described.

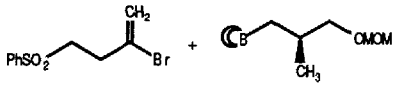
Amphidinolide-A (**1**) was isolated from dinoflagellate *Amphidinium sp.* by Kobayashi et. al[1]. This compound has shown *in vitro* activity against L1210 (IC_{50} 2.4 ng/mL) murine leukemia cells.[2] Compound **1**, although structurally similar to swineholide A[3a] and scytophycin B,[3b] possesses some unusual features. For example, the three exocyclic methylene groups in the macrolide ring appear to be unique. The four hydroxyl groups attached to the macrocycle are situated close enough together to form a hydrophilic region. Neither the relative nor the absolute stereochemistry at the nine chiral centers in this molecule has yet been reported. Hence, we set out to develop synthetic methodology suitable for the preparation of all possible stereoisomers in order to make an unambiguous assignment of the stereochemistry and to complete a total synthesis of amphidinolide-A. As an initial step towards these two goals, we present the synthesis of a suitably protected, optically pure (10S, 11R, 17R) C_{10}-C_{19} (amphidinolide-A numbering) fragment **2**.



1 2 3 4

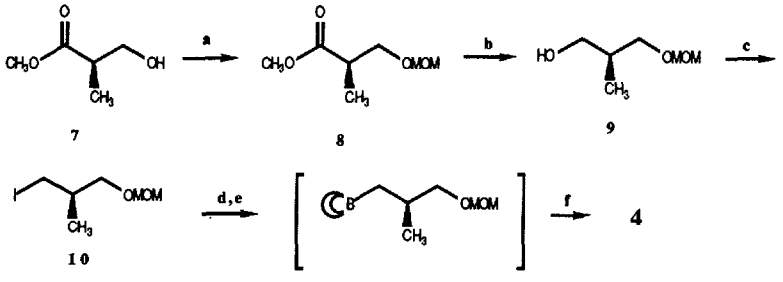
For the preparation of optically pure **2**, we determined that the key step was construction of the C_{13}-C_{14} *trans* olefin. We chose to utilize the Julia olefination procedure since it gave us best results among numerous olefin forming reactions which we investigated.[4] Thus, the necessary components, ester **3** and sulfone **4**, were required.

The optically pure ester **3** is readily available as either enantiomer from (+) or (-)-tartaric acid. For our initial investigation we chose to utilize (+)-tartaric acid. Hence optically pure **3**, ($[\alpha]_D$= - 8.30, neat) was prepared by the literature method.[5] However, the sulfone **4** had not previously been prepared, and its synthesis required a more elaborate strategy. After examining several different syntheses of **4**, we concluded that the most effective synthesis employs the recently described procedure of Suzuki[6]. Suzuki's procedure utilizes palladium complexes to effect regiospecific coupling of alkyl boranes with vinylic bromides. Hence, sulfone **5** and borane **6** are the precursors to **4**. At first glance, optically active borane **6** appeared easily accessible by chiral hydroboration of a methallyl alcohol derivative. However, it is well documented that poor chiral induction is obtained from chiral hydroboration of 2-methyl-1-alkenes.[7] This fact precluded our use of a chiral hydroboration reaction and forced us to find an alternative method to obtain pure enantiomers of **6**.



5 **6**

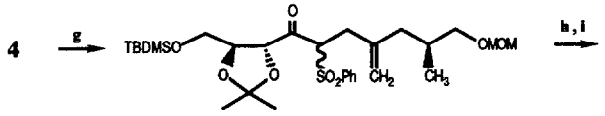
Starting with commercially available S-(+)-methyl 3-hydroxy-2-methylpropionate (**7**), we prepared the iodide **10** in three steps as shown below.[8] The methoxymethyl protected alcohol **9** was prepared in 95% yield from **7** in two steps by a slight modification of the literature procedure.[9] Conversion of **9** to the optically pure iodide **10** ($[\alpha]_D$= + 4.77) proceeded in 86% yield. Treatment of the iodide **10** with two equivalents of t-butyllithium in ether/pentane at -78° C gave a lithium reagent which was then converted to **6** by addition of B-methoxy-9-BBN (-78° C to 0° C). Reaction of **6** with **5** (prepared from methyl phenyl sulfone and 2,3-dibromopropene)[10] in DMF with 3 mol % dichloro-[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) (Cl_2Pd(DPPF)), at 60° C for 16 hours gave the desired sulfone **4** in 84% yield ($[\alpha]_D$= -0.83).



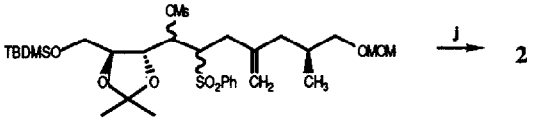
7 **8** **9** **10**

Reagents and Conditions: a) MOMCl (1.5 eq), iPr_2NEt (1.5 eq), CH_2Cl_2, rt 12 hrs, b) LAH/THF 0° C to rt 8 hrs, (95% from **7**), c) Ph_3P (1.2 eq), I_2(1.2 eq), Imidazole (3 eq), C_6H_6, 50° C 6 hrs, (86%), d) t-BuLi (2 eq), Et_2O/ pentane -78° C 30 min, e) B-OCH_3-9-BBN (1 eq), -78° C 1hr, then 0° C 1hr, f) **5** (0.91 eq), 3 mol % Cl_2Pd(DPPF), K_2CO_3 (3 eq), DMF 60° C 16 hrs, (84%)

The coupling of the two segments **3** and **4** was completed as follows. One equivalent of the sulfone **4** was treated with one equivalent of n-butyllithium at -78° C and 0.5 equivalents of the ester **3** and then warmed to room temperature. The mixture was recooled to -78° C whereupon 0.5 equivalents of LDA was added followed by another 0.5 equivalents the ester **3**. This procedure gave the β-ketosulfone **11** in 65% yield.[11] Reduction of **11** with $NaBH_4$ was followed by mesylation (mesyl chloride/Et_3N) to yield the mesylate **12**. Reaction of **12** with 5% Na(Hg) in CH_3OH buffered with Na_2HPO_4 at -20° C gave the desired fragment **2**[12] ($[\alpha]_D$= -4.42) in 69% overall yield from the ketosulfone **11**. This step completes our development of a suitable reaction sequence leading to a potential C_{10}-C_{19} fragment of amphidinolide-A.



11



12

Reagents and Conditions; g) 1) n-BuLi/THF (1 eq), -78° C, **3** (0.5 eq), -78° C 5 min then 0° C 1 hr, 2) LDA/THF (0.5 eq), -78° 30 min then **3** (0.5 eq), -78° C to rt 2 hr, (65%), h) $NaBH_4$ (3 eq), EtOH rt 1 hr, i) Mesyl Chloride (1.2 eq), Et_3N (3 eq), CH_2Cl_2 0° C 3 hr, j) 5% Na(Hg), Na_2HPO_4, MeOH -20° C 1hr, (69%) from **11**.

To date all of the reactions described herein have been carried out on a scale of at least 1 mM. Several reactions have been performed on a multigram scale with no significant changes in yield.

It will clearly be possible to utilize the reaction sequences described herein (i.e. starting from (+) or (-) **-7** and (+) or (-)-**3**) to prepare alternative optically pure stereoisomers of the diene **2**.[13] Perhaps one of these other stereoisomers of **2** will be necessary to complete the total synthesis and stereochemical assignment of **1**. Studies are currently underway to elaborate **2** (or a suitable stereoisomer thereof) into amphidinolide-A, and thereby unambiguously assign the stereochemistry of this natural product.

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8 We note that the R(-)-enantiomer of **7** is also commercially available at about the same price as the S-(+) isomer.

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12 The spectral data are as follows: **Compound 4**: ^{1}H-nmr (400 MHz $CDCl_3$): δ0.86 (d, 3H, J = 6.5 Hz); 1.77 (m, 1H); 1.84 (m, 1H); 2.17 (m, 1H); 2.41 (m, 2H); 3.23 (m, 2H); 3.30 (m, 2H); 3.34 (s, 3H); 4.58 (s, 2H); 4.75 (s, 1H); 4.79 (s, 1H); 7.55-7.95 (m, 5H). ^{13}C-nmr (100 MHz $CDCl_3$): δ16.8; 28.4; 31.5; 40.4; 54.8; 55.1; 72.6; 96.6; 112.5; 128.1; 129.3; 133.8; 139.1; 143.7. ir (neat) (cm $^{-1}$): 1644.7; 1446.1; 1307.9; 1149.6; 1043.1: 919.4. HRMS/CI (isobutane) M + 1: calc. 313.14374; anal. 313.1474. **Compound 3**: ^{1}H-nmr (400 MHz $CDCl_3$): δ0.08 (s, 6H); 0.09 (s, 9H); 1.45 (s, 3H); 1.46 (s, 3H.); 3.78 (s, 3H); 3.80 (d of d, 1H, J = 11.1, 4.0 Hz); 3.89 (d of d, 1H, J = 11.1, 3.6 Hz); 4.21 (d of d of d, 1H, J = 7.4, 4.0, 3.6 Hz); 4.91 (d, 1H, J = 7.4 Hz). ^{13}C-nmr (100 MHz $CDCl_3$): δ -5.4; -5.3; 18.4; 25.9; 26.9; 52.3; 62.8; 75.4; 79.8; 111.4; 171.4. ir (neat) (cm $^{-1}$): 2954; 2930; 2858; 1763; 1460, 1382; 1255; 1205; 1145; 1107; 838. HRMS/CI (isobutane) M + 1; calc. 305.178375; anal. 305.1763. **Compound 2**: ^{1}H-nmr (400 MHz $CDCl_3$): δ0.06 (s, 3H); 0.07 (s, 3H); 0.90 (s, 9H); 0.92 (d, 3H, J = 6.6 Hz); 1.41 (s, 3H); 1.42 (s, 3H); 1.82 (m, 1H); 1.93 (m, 1H); 2.18 (m, 1H); 2.75 (m 2H); 3.31 (d of d, 1H, J = 9.2, 6.4 Hz); 3.35 (s, 3H); 3.38, (d of d, 1H, J = 9.2, 6.5 Hz);3.69 (d of d, 1H, J = 10.0, 3.4 Hz); 3.74 (m, 1H) 3.78 (d of d, 1H, J = 10.0, 3.3 Hz); 4.34 (m, 1H); 4.61 (s, 2H); 4.79 (m, 2H); 5.52 (d of d, 1H, J = 15.3, 7.6 Hz); 5.79 (m, 1H). ^{13}C-nmr (100 MHz $CDCl_3$): δ -5.4; -5.3; 17.0; 25.9; 26.9; 27.2; 29.7; 31.5; 38.8; 40.0; 55.1; 73.0; 78.7; 81.6; 96.6; 108.9; 112.1; 129.2; 132.3; 145.8. ir (neat) (cm $^{-1}$): 2923; 1644; 1463; 1379; 1253; 1146; 1046; 837.

13 We note that the four additional optically pure stereoisomers of **2** are easily accessible by the reaction sequence described herein. To obtain any of the four additional stereoisomers, we are required to start with an optically pure diastereomer of the triol ester **3**. These compounds are readily available from either (D)-isoascorbic acid (see Cohen et. al, *J. Am. Chem. Soc.*, 1983, **105**, 3661.) or from *dl*-erythronic acid. (Glattfeld, J. W. E.; Forbrich, L. R., *J. Am. Chem. Soc.*, 1934, **56**, 1209.).

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